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Efficacy of smoking cessation therapy alone or integrated with prolonged exposure therapy for smokers with PTSD: Study protocol for a randomized controlled trial

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Abstract

Posttraumatic stress disorder (PTSD) is related to an increased risk of smoking cessation failure. In fact, the quit rate in smokers with PTSD (23.2%) is one of the lowest of all mental disorders. Features of PTSD that contribute to smokers' progression to nicotine dependence and cessation relapse include negative affect, fear, increased arousal, irritability, anger, distress intolerance, and anxiety sensitivity. Anxiety sensitivity is higher in people with PTSD than in any other anxiety disorder except for panic disorder. High anxiety sensitivity is uniquely associated with greater odds of lapse and relapse during quit attempts. Distress intolerance, a perceived or behavioral tendency to not tolerate distress, is related to both the maintenance of PTSD and problems in quitting smoking. Prolonged exposure (PE) and interoceptive exposure (IE) reduce PTSD symptoms, distress intolerance, and anxiety sensitivity. Thus, they emerge as promising candidates to augment standard smoking cessation interventions for individuals with PTSD. The present study tests a 12-session specialized treatment for smokers with PTSD. This Integrated PTSD and Smoking Treatment (IPST) combines cognitive-behavioral therapy and nicotine replacement treatment for smoking cessation (standard care; SC) with PE to target PTSD symptoms and IE to reduce anxiety sensitivity and distress intolerance. Adult smokers ($N = 80$) with PTSD will be randomly assigned to either: (1) IPST or (2) SC. Primary outcomes are assessed at weeks 0, 6, 8, 10, 14, 16, 22, and 30.

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1. Introduction

Cigarette smoking is the leading cause of death and disability in the United States (U.S.), contributing to over 440,000 deaths each year [65]. Rates of tobacco use in the U.S. represent a significant public health concern with approximately 45–48 million adults who currently use tobacco [15]. Though approximately 70% of current adult smokers are motivated to quit [65], approximately 90–95% of smokers who try to quit smoking on their own [29], and 60–80% who attend treatment programs, relapse to smoking [13]. Notably, persons diagnosed with psychiatric and substance abuse disorders are 2–3 times more likely to be dependent on tobacco and die up to 25 years earlier than the general population [66]. One possible explanation is the selection hypothesis of smoking prevalence which posits that smokers who are able to quit successfully are not “burdened” by specific characteristics that make it more challenging to quit [37], including medical or psychiatric illnesses. One such high-risk group is individuals with anxiety disorders.

Smokers with a history of anxiety disorders experience significant challenges quitting tobacco [68,69] yet little attention has been paid to the maintenance of tobacco use among persons with anxiety disorders, and in particular, smokers with PTSD. PTSD is a common mental disorder, with lifetime prevalence in the USA of 6.8% [40,41]. The prevalence of current smoking in persons with current PTSD is 44.6%, compared to 22.5% in persons who had never had a psychiatric disorder [43]. Smokers with PTSD are more likely to be dependent [11], to smoke heavily (>25 cigarettes per day [5]), to experience more severe withdrawal symptoms, and to relapse following a quit attempt [5]. Furthermore, the quit rate in smokers with PTSD is one of the lowest among groups defined by specific mental disorders [43]. The PTSD-smoking association observed in epidemiological surveys appears to reflect primarily the influence of pre-existing PTSD on the risk for subsequent smoking progression and transition to nicotine dependence [10,11,42]. Specific features of PTSD may contribute to smokers' progression to nicotine dependence and relapse including negative affect, fear, anxiety sensitivity, increased arousal, irritability, and anger. Thus, isolating the specific vulnerability mechanisms linking PTSD to smoking cessation problems may aid identification of possible therapeutic targets.

Some of the strongest and most consistent evidence contributing to tobacco use has been evident for anxiety sensitivity and distress intolerance [7]. These two constructs are conceptually and empirically distinct (i.e. sharing only 15–22% of variance with one another [7]), yet, they both are elevated among those with PTSD [7,46,60], can be targeted in treatment and changed [55] and tend to be related to cognitive-affective reactivity as well as emotional regulatory deficits of central theoretical and clinical relevance to smoking cessation [70]. Thus, they represent distinct mechanisms potentially underlying PTSD-smoking relations. These findings are consistent with contemporary theoretical models of smoking behavior [3].

As outlined above, improving cessation outcomes among individuals with PTSD may require reducing PTSD symptoms as well as anxiety sensitivity and distress intolerance that increase risk of relapse. Fear extinction-based treatments (i.e., prolonged exposure [PE], interoceptive exposure [IE]) have shown efficacy for reducing PTSD distress intolerance, and anxiety sensitivity [18,57,64] and therefore emerge as promising candidates to augment standard smoking cessation interventions for individuals with PTSD. Initial studies suggest a combined treatment approach for this population is worth further study. First, Felder, Smith, Monson, and Zvolensky [25] conducted a multiple-baseline study with six smokers with PTSD [25]. The intervention (12 50-minute sessions) included CBT for smoking and trauma-focused therapy for PTSD. Results showed small but significant reductions in PTSD symptoms, but only temporary reductions in smoking. Recommendations include a higher dose of PTSD/smoking treatment, adding more interoceptive exposure, and intent-to-treat analyses. Second, Gonzalez et al. [31] randomized 90 smokers with PTSD to smoking cessation alone or in combination with a trauma management program [31]. The trauma program (8 90-minute sessions) included interoceptive exposure, cognitive restructuring, and in-vivo exposure to trauma cues. Overall, results showed no significant difference between groups in PTSD symptom or smoking improvements. Recommendations include a higher dose of PTSD/smoking treatment. Also, this study did not include imaginal trauma exposure. The present study proposes to test an intervention that integrates PE and IE with standard cessation treatment among adults suffering from PTSD. More specifically, we will use a higher dose intervention (12 90-minute sessions), add imaginal trauma exposure, and add interoceptive exposure.

Drawing from basic research and stage-model treatment development work over the past decade, we have developed the Integrated PTSD and Smoking Treatment (IPST). IPST represents an integrated treatment that incorporates elements of intensive standard smoking cessation treatment with exposure-based procedures for reducing PTSD symptoms and associated AS, as well as enhancing tolerance to aversive internal sensations. The IPST protocol involves twelve weekly 90 minute sessions and was designed for use in conjunction with nicotine replacement therapy (NRT). In addition to PE for PTSD symptoms, aspects of IPST that uniquely focus on addressing fears of anxiety, bodily-related sensations, and affect-relevant withdrawal symptoms include: (1) interoceptive exposure (i.e., repeated exposure to feared bodily sensations) with (2) corrective information about anxiety and cognitive interventions designed to teach patients alternatives to catastrophic misinterpretations of the sensations and their feared consequences (“I will lose control”), as well as (3) continued use of situational exposure. Specifically, cognitive restructuring is aimed at eliminating catastrophic beliefs about the meaning and consequences of anxiety and PTSD symptoms as well as symptoms of withdrawal. Additionally, interoceptive exposure is employed to extinguish fears of aversive internal sensations regardless of their source, but with specific preparation for sensations that would be experienced as part of smoking discontinuation (withdrawal). The goal is not to attempt the impossible task of eliminating anxiety or emotion-laden withdrawal sensations but rather to ensure that these internal cues are not interpreted fearfully, escalating bothersome sensations into debilitating panic and related negative affect symptoms. Exposure to such symptoms in advance of cessation should help to ensure that participants have practice with an alternative model of

symptom management well before the characteristic symptoms of smoking discontinuation are encountered.

The primary aim of the proposed study is to obtain estimates of the relative efficacy of the integrated treatment for smokers with PTSD (IPST) compared to a smoking cessation only control condition (SC). The secondary aim is to perform an initial examination of the putative mechanisms underlying the hypothesized advantage of the integrated treatment. To this end, we will conduct a randomized controlled trial comparing the relative benefit of IPST over SC.

2. Methods

The Institutional Review Board of University of Texas at Austin approved this study and a Data Safety and Monitoring Board provides ongoing monitoring. This study is funded by the National Institutes of Health 1K01 grant number DA035930-01 and is registered on clinicaltrials.gov (ID: NCT01988935). This study is currently in the recruitment phase (year 3 of 5). The study is currently conducted at a single site at the University of Texas at Austin.

2.1. Specific aims & hypotheses

1. To compare, in a randomized clinical trial, the effects of IPST vs. SC on the following smoking cessation outcomes:
 - A. We expect that point prevalence abstinence (PPA) will be higher, both in the short- and long-term, in the IPST condition than in the SC condition. Similarly, we expect the rate of decline in abstinence over time to be smaller in the IPST condition than in the SC condition.
 - B. We expect mean time to first lapse and to relapse to be greater in the IPST condition than in the SC condition.
2. To compare, in a randomized clinical trial, the effect of IPST vs. SC on psychological symptoms, including PTSD symptoms, depressive symptoms, anxiety sensitivity, and distress tolerance:
 - A. We expect that psychological symptoms will be lower at post-treatment and follow-up in the IPST condition than in the SC condition.
 - B. We expect that treatment condition differences in psychological symptoms will mediate treatment condition differences in abstinence at both post-treatment and follow-up.
3. Exploratory aim: To determine if the advantage of IPST over SC on smoking outcomes is greater for those with greater baseline PTSD severity. PTSD severity is related to severity of depressive symptoms, distress tolerance, and anxiety sensitivity, and each of these is related to abstinence. Thus, individuals with low baseline PTSD severity are likely to have only modestly elevated levels of these psychological barriers to abstinence, and hence may benefit only minimally from the PTSD treatment in IPST. Those with high baseline PTSD severity, however, are likely to have significantly elevated levels of depressive symptoms, distress

intolerance, and anxiety sensitivity, and hence can benefit greatly from IPST that is designed to reduce these symptoms.

2.2. Power analysis

Because we will have a sample size of 80, this application is not powered to detect small differences between treatment conditions. However, consistent with the aims of a Stage IB study, our primary goal is determining 1) the feasibility of the new intervention and 2) whether a Stage II study is warranted. Below we estimate (for the lowest powered analyses) the effect sizes (ESs) that we will be able to detect as statistically significant with 80% power.

2.2.1. Aim 1a: GLMM model comparing PPA in the IPST condition vs. the SC condition—Because there are no power analysis programs available to calculate the power for complicated GLMM models, we performed a Monte Carlo study to calculate the minimum IPST PPA rate detectable by our analysis. Our assumptions were: participants provide data at 70% assessments and that the PPA rate in SC is 27% at the last follow-up. We examined numerous IPST PPA rates to determine the lowest rate detectable by our analysis, performing 1000 simulations for each PPA rate. The results indicated that we would have 0.80 power to detect a significant treatment effect if the PPA rate in IPST at the follow-up was 43% or greater. This difference – i.e., 43% vs. 27% – is equivalent to a Cohen's w effect size (the effect size measure for proportions) of 0.17, between a small (0.10) and medium (0.30) ω effect size [16]. Thus, we have sufficient power to detect a smaller than medium effect.

2.2.2. Aim 2b: mediation of treatment condition differences in abstinence—We performed a Monte Carlo study to calculate the power for a bootstrap mediation analysis. We assumed that the effect sizes for the “a” paths (the change in the mediators over time) would be large ($ds > 0.80$), the effect size for the “b” paths would be medium. The Monte Carlo study consisted of 400 samples, for each of which we performed a bootstrap mediation analysis each consisting of 1000 resamples. Results indicated that we would have at least 0.81 power to detect a mediated effect.

2.3. Overview

Eighty adult smokers with PTSD will be randomized to receive either an Integrated PTSD and Smoking Treatment (IPST) or standard smoking cessation treatment (SC). All participants will meet individually with a study therapist once weekly for 12 weeks and will be asked to make a quit attempt at week 6. Participants will be offered Nicotine Replacement Therapy (NRT) in the form of the patch to use alongside their designated condition. Smoking cessation outcomes will be measured up to 6-months following this proposed quit date (see Fig. 1).

2.4. Participants

Participants will be males and females with PTSD between the ages of 18 and 65, who have been daily smokers for at least three months, currently smoking an average of at least 8 cigarettes per day and who are motivated to quit smoking. Each individual will be screened

with the Structured Clinical Interview for DSM-IV Non-patient Edition (SCID-NP) to determine that they meet criteria for PTSD. Sufficient motivation to quit will be operationalized as a self-reported level of motivation of at least a 5 on a 10-point scale (0 = not at all motivated, 10 = extremely motivated). In addition, participants must be willing and able to provide informed consent, understand inclusion and exclusion criteria, and accept the randomized group assignment.

To preserve high internal validity and reduce risk of adverse events, we will employ the following exclusion criteria: (1) current diagnosis of a psychotic, eating, developmental or bipolar disorder; (2) significant suicide risk as determined by structured interview; (3) psychoactive substance dependence (excluding nicotine dependence) within the past 3 months; (4) limited mental competency and the inability to give informed, voluntary, written consent to participate; (5) current use of any pharmacotherapy or psychotherapy for smoking cessation not provided by the researchers during the quit attempt; (6) current psychotherapy directed specifically toward treatment of PTSD; (7) planning on moving (outside of the immediate area) in the next six months; and (8) insufficient command of the English language (i.e., they cannot carry on a conversation with an interviewer in the English language or read associated text).

2.4.1. Screening and randomization—An online prescreen will be conducted to determine possible eligibility for all potential participants who respond or are referred via various recruitment strategies. Recruitment strategies include posting brief advertisements describing the study in social media outlets, craigslist, and newspapers. All recruitment advertisements were approved by the IRB. The online prescreen will be used as the initial screening method to assess level of motivation to quit, smoking behaviors, and trauma history. All online data, including the prescreen will be collected through REDCap (Research Electronic Data Capture), an electronic data-capture tool hosted at University of Texas at Austin [35]. Individuals who appear eligible based on the online prescreen will then be contacted via phone to verify smoking history and further assess eligibility based on the traumatic experience. Those deemed eligible after the telephone screen will then be invited to a longer screening session with a trained staff member to be conducted either by phone or in person. Studies show equivalent reliability and validity of diagnostic interviews delivered via phone compared to in person [17,19,45]. Participants will be sent an electronic consent form and asked to complete an online survey collecting demographic information and assessing medical history to determine that individuals are in sufficiently good health to participate in interoceptive exposures. Participants will then be screened using the SCID-NP to confirm a diagnosis of PTSD and assess for the aforementioned diagnostic exclusions. The Columbia Suicide Severity Rating Scale (C-SSRS) [52] will then be administered to exclude participants experiencing significant suicidal ideation for whom participation in the trial could prove to be an additional stressor. Participants excluded for significant suicidal ideation will be provided with appropriate resources.

2.4.2. Baseline/randomization—Participants deemed eligible after the screening session will be invited to a baseline assessment. Baseline assessments will include assessments of blood pressure, pulse, height, weight, motivation to quit, and expired air carbon monoxide

levels (assessed with a carbon monoxide monitor; Smokerlyzer® by coVita). In addition, smoking history over the previous seven days will be collected via timeline follow-back procedure [2], and participants will complete a battery of online assessments (for assessment schedule, see Table 1). Participants will also meet with their study therapist, receive an orientation to the study, and be informed of their condition assignment. The project statistician oversees the randomization process to either IPST or SC conditions, using variable-sized permuted block randomization. Prior to data analyses, the project statistician will check the balance of randomization and control for any factors that are imbalanced. Additionally at baseline, an independent evaluator conducts the Posttraumatic Symptom Scale – Interview Version (PSS-I) [28] and Clinical Global Impression – Global Improvement Scale (CGI-I) [32] with participants.

2.5. Interventions

2.5.1. Standard smoking cessation treatment (SC)—All participants will receive standard smoking cessation treatment as administered in past protocols [56]. This will consist of cognitive behavioral treatment (CBT) for smoking cessation combined with nicotine replacement therapy (NRT) in the form of nicotine patches. This standard treatment will be delivered once-weekly 45-minute sessions over a 12-week period (see Fig. 1). The first six-weeks of SC are designed to plan and prepare the individual for their upcoming quit day (see Table 2). Topics discussed include learning from past quit attempts, self-monitoring of cigarette consumption, identifying and preparing for high-risk situations, utilizing coping strategies when experiencing smoking urges, enlisting social support, and utilizing self-help materials. Week 6 of the protocol will be designated as the “quit day,” at which participants will be encouraged to make their first quit attempt and will be given the option of beginning NRT. Participants will be offered Nicoderm CQ®, 24-hour transdermal nicotine patches in dosages corresponding with their cigarette count of the week leading up to their quit day and educated about the use of the patch at the session immediately prior to quit date. Participants will be provided with up to 8 weeks of NRT based on guidelines suggesting 8 weeks of NRT is as efficacious as longer treatment periods. The step-down dosage schedule is as follows: 1) 4 weeks of 21 mg/day, 2) 2 weeks of 14 mg/day, and 3) 2 weeks of 7 mg/day. While participants are using the patch, the study therapist will assess for any side effects they may experience. Participants will be informed that they may also elect to start at a lower dose, not use the patch at all, and may discontinue use of the patches at any time. Participants who lapse or relapse will be encouraged to set a new quit date and continue their cessation attempt.

2.5.2. Integrated PTSD and Smoking Treatment (IPST)—IPST is a 12-week program involving once-weekly 90-minute sessions (see Table 2). IPST treatment represents an optimized protocol that incorporates elements of standard smoking cessation treatment (as discussed previously) with therapy for reducing PTSD symptoms and anxiety sensitivity and enhancing tolerance for nicotine withdrawal sensations (see Table 2). IPST uniquely focuses on addressing PTSD symptoms, fears, and intolerance of anxiety, bodily-related sensations, and affect-relevant withdrawal symptoms through: (1) imaginal exposure to the trauma memory, (2) in-vivo situational exposure, (3) interoceptive exposure, and (4) corrective information about anxiety and cognitive interventions designed to teach patients

alternatives to catastrophic misinterpretations of the sensations and their feared consequences. Particularly novel here is that we are asking patients to remain cigarette-free three-hours prior to certain sessions before the quit date. Indeed, this allows for direct extinction training during the session (where emotional cues are induced and no smoking occurs). This training can ensure absence of a contingency between emotional induction and cigarette use. Table 2 provides a session-by-session outline and illustrates the integrated nature of this hybrid treatment.

2.6. Post-treatment follow-up

Participants will be contacted to complete follow-up assessments at weeks 14, 16, 22, and 30. Table 2 provides an overview of measures utilized at each of these follow-up time points. Follow-up assessments will consist of a brief (approximately 10–15 min) check-in by the study therapist with the participant as well as a separate meeting with the independent evaluator to conduct an assessment of PTSD symptom severity (see below). Follow-up assessments will be conducted in person so as to collect biochemical data confirming smoking abstinence.

2.7. Assessment

Fig. 1 and Table 2 provides an overview of the frequency and timing of administration for the primary assessment instruments used for screening, to measure post-cessation smoking outcomes, PTSD severity, putative mediators, and to measure treatment integrity and acceptance.

2.7.1. Primary outcome measures – measures of smoking status

2.7.1.1. Abstinence: We will use the timeline follow-back (TLFB; [59]) procedure to assess cigarette consumption at each day following the previous assessment. We have previously used the TLFB to assess cigarette use among high anxiety sensitivity smokers [47,53,58] and the assessment has demonstrated good reliability and validity [12]. Self-reported abstinence at every assessment will be verified by expired carbon monoxide (CO). Abstinence at follow-up sessions following the quit day will additionally be verified with saliva cotinine. Self-reported abstinence will be overridden by a positive carbon monoxide (N8 ppm) or saliva cotinine verification (>10 mg/mL) [56]. If neither CO nor cotinine levels were available to verify abstinence at an assessment, abstinence will be considered missing data [9]. As in past work [56], we will employ 7-day point prevalence abstinence (PPA) and prolonged abstinence (PA) as the primary outcomes. PPA will be defined as no smoking, not even a puff, in the 7 days prior to any assessment. Failure to maintain PA at any assessment will be defined by 7 or more consecutive days of smoking or smoking at least 1 cigarette over the 2 consecutive weeks prior to the assessment. Because some participants will quit before the target quit day (week 6), the starting point for measuring abstinence will be at baseline.

2.7.1.2. Biochemical verification: Self-reported abstinence at the 16- and 24-week follow-ups will be verified by saliva cotinine (cutoff value of 10 mg/mL) for stated abstinence of 2 weeks or more (cotinine may be incompletely metabolized before this time), and carbon monoxide analysis of breath samples (8 ppm cutoff) for stated abstinence of 24 h to 2 weeks

[70]. Saliva samples will be frozen and analyzed by an outside laboratory for cotinine level using radioimmune assay. Expired air carbon monoxide levels will be assessed with a Smokerlyzer® by coVita carbon monoxide monitor. Detected values above the stated cutoff scores will be considered indicative of smoking.

2.7.2. Secondary outcome measures – measures of PTSD, mood, and anxiety symptoms and side effects

2.7.2.1. PTSD Symptom Scale-Interview Version (PSS-I; [28]): This interviewer administered 17-item scale rates each of the DSM-IV symptom criteria on a 0–3 scale of frequency and/or severity. The PSS-I is a reliable and valid scale; it is sensitive to treatment effects and is highly correlated with another widely used Clinician Administered PTSD Scale (CAPS) [8].

2.7.2.2. Posttraumatic Stress Diagnostic Scale (PDS; [27]): This self-report questionnaire is a widely used psychometrically-sound 17-item scale for the assessment PTSD symptom severity.

2.7.2.3. Anxiety Sensitivity Index-III (ASI-III; [61]): The ASI-III is a psychometrically-sound 18-item self-report measure in which respondents rate their degree of concern about experiencing anxiety-related sensations. This measure has been validated among a smoking population [23].

2.7.2.4. Distress Tolerance Scale (DTS; [54]): The DTS is a 14-item psychometrically-sound self-report measure on which respondents indicate their perceived ability to tolerate emotional distress [44].

2.7.2.5. Beck Depression Inventory (BDI; [4]): The BDI is a widely used 21-item, self-report inventory designed to measure severity of depressive symptoms.

2.7.3. Other measures

2.7.3.1. Motivation to Quit Smoking: Participants will be asked to report their motivation to quit smoking on a 10-point scale (0 = no motivation, 10 = extremely motivated to quit).

2.7.3.2. Smoking Abstinence Expectancy Questionnaire (SAEQ; [1]): The SAEQ is a 28-item self-report measure of expected consequences of 24-h of smoking abstinence.

2.7.3.3. Fagerström Test for Nicotine Dependence (FTND; [36]): The FTND is a 6-item scale designed to measure severity of tobacco dependence. The FTND has shown adequate levels of internal consistency, positive relations with key smoking variables (e.g., saliva cotinine; [36,49]), and high degrees of test-retest reliability [51].

2.7.3.4. Minnesota Withdrawal Scale: The Minnesota Withdrawal Scale (MWS) is a 10-item scale that measures withdrawal symptoms and has been found to be reliable and sensitive [38,50].

2.7.3.5. Reasons for Quitting Questionnaire (RFQ): The RFQ [20] is a 20-item self-report measure on which respondents indicate the extent to which each of the reasons for smoking cessation applies to them at the time of administration. The RFQ was used to assess motivation to quit smoking. The RFQ has been found to have satisfactory internal consistency and predictive validity [20].

2.7.3.6. Questionnaire of Smoking Urges – Brief Version (QSU – Brief; [62]): The QSU is a 10-item measure that assesses urges and cravings for cigarettes [67]. This assessment of urges can be used to evaluate consistency (or lack thereof) with withdrawal symptoms in follow-up tests from the data set.

2.7.3.7. Acceptance and Inflexibility Scale (AIS; [30]): The AIS is a 13-item measures designed to evaluate smoker's endorsement of avoidance strategies related to smoking and smoking cessation. The scale has been validated in a smoking population [24].

2.7.3.8. Credibility and Expectance Questionnaire (CEQ; [21]): The CEQ is a 6-item scale for measuring treatment expectancy and rationale credibility of the protocol. The questionnaire was found to have high internal consistency with each factor and good test-retest reliability.

2.7.3.9. Smoking History Questionnaire (SHQ; [14,67]): The SHQ, a 26-item self-report measure, assesses the respondent's rate of smoking, age at initiation of smoking, number of years as a regular smoker, brand of cigarettes, total number of previous serious quit attempts, and other smoking history behaviors and patterns.

2.7.3.10. Demographics: Participants will be asked to provide demographic information including age, gender, race/ethnicity, marital status, occupational level, educational level, income level, and occupational status.

2.7.3.11. General health history: Self-reported health history will be obtained at the screening assessment to collect information regarding history of medical diagnoses, medical treatment, and medication use.

2.7.3.12. Psychiatric diagnosis: Lifetime prevalence of Axis I diagnoses including PTSD diagnosis and exclusion criteria will be assessed using the Structured Clinical Interview for DSM-IV Non-patient Edition [26] by a trained study therapist. All diagnostic interviews will be supervised by the first author.

2.7.3.13. Suicidality: The Columbia Suicide Severity Rating Scale (C-SSRS; [52]) will be administered to assess for current and past suicidal ideation, intent, and behavior as well as self-injurious non-suicidal behaviors. The C-SSRS demonstrates good reliability and validity [34,52].

3. Data analysis

The primary aim of this Stage 1B study is to obtain estimates of treatment effect size (ES), which is crucial to establishing efficacy and planning for a future Stage II trial. ES will be

calculated for odds ratios for PPA, relative risks in survival analyses for time to first smoking, and differences in slopes of improvement for both PPA and psychological symptoms. A sample size of 80 will also allow us to evaluate the efficacy of the intervention.

We will assess the equivalence of the treatment groups on key baseline variables (demographics, smoking characteristics, psychological variables); variables on which the groups differ will be used as a covariate in final analyses. We will then examine missing data patterns, dropout rates (see below), and distributional properties of measures and use transformations to improve distributions when necessary.

3.1. Aim 1—Following recommendations of the Society for Research on Nicotine and Tobacco [33], the effects of treatment on abstinence (herein, abstinence refers to both PPA and PA) will be examined using Generalized Linear Mixed Models (GLMM), employing the logistic linking function. In our GLMM analyses, the repeated measures will be nested within individuals, which will be nested within their treatment cohort, thereby appropriately accounting for correlated scores within the small cohorts. As in our previous research with a similar intervention schedule [56], we will use a 3-phase piecewise growth curve model to track abstinence over the 30-week study. The first phase of the growth model will consist of weeks 0–6 (pre-quit treatment phase), the second phase will be weeks 7–12 (post-quit treatment phase), and the third phase will be weeks 13–30 (follow-up phase). Modeling the growth curve starting at week 0 is necessary for intent-to-treat analyses. We will model change over time as curvilinear within each phase, but drop curvilinear terms if they are not significant. We will also model a discontinuity in the growth curve between the first and second phase to reflect the expected effects of the scheduled quit day during week 6.

Treatment condition will be modeled as a predictor of the slope of change in abstinence during each phase of the study, and as a predictor of the discontinuity. Because we expect treatment dose to predict abstinence (as was the case in our recent smoking cessation study [56]), and to reduce variance in abstinence related to treatment dose, we will also include Session Attendance and Session Attendance $\times$ Treatment Condition as moderators of the slopes during each phase of the study. Nonsignificant interaction terms will be dropped and the final model recomputed. We will also run a Cox proportional hazards survival analysis predicting risk of lapsing or relapsing to smoking and compare the two conditions on these outcomes. For these models, lapse and relapse were defined consistent with previous research [39,48]). A lapse is defined as any smoking (even a puff) since the last assessment. A relapse is defined as seven consecutive days of smoking since the last assessment.

3.2. Aim 2—Multi-level models (MLMs) will be used to test treatment differences in the psychological outcomes (PTSD severity, depressive symptoms, distress intolerance, and anxiety sensitivity). These MLMs will be 2-phase piecewise growth curve models (treatment phase (weeks 0–12) and follow-up phase (weeks 13–30). They will not be 3-phase models like the ones for abstinence because quit week will not result in a discontinuity between weeks 6 and 7 in the psychological variables as it does on abstinence. We will select the growth curve during each phase that best fits the data based on AIC and BIC criteria. All models will include relevant control variables (e.g., gender, education, nicotine dependence, etc.). Because we have four psychological outcome variables, we will use the Benjamini-

Hochberg [6] method to correct for the possible inflation of Type 1 error due to multiple significance tests [6].

The mediation analysis that we will perform is commonly referred to as “level 1 mediation of a level 2 effect”. The “level 2 effect” that is mediated is the between-subjects effect of treatment condition, a “level 2” variable, on abstinence. “Level 1” mediation refers to the fact that the mediators and outcomes are assessed repeatedly at every assessment point, and hence the relations between the mediators and abstinence are within-subjects, longitudinal relations over time. To perform this mediation analysis, we will add all four psychological variables (PTSD severity, depressive symptoms, distress intolerance, and anxiety sensitivity) simultaneously as time-varying predictors in the GLMM model for abstinence (in Aim 1). To establish temporal precedence, the psychological variables at each time point will predict abstinence at the next time point. The regression coefficient for each of these psychological variables will provide the “b” paths in the mediation model (see Fig. 2). Adding all four variables simultaneously to the GLMM will allow us to determine if each variable mediates treatment condition differences in abstinence over and above the others. The “a” paths in the mediation model will be calculated using the MLMs in Aim 2. The significance of each mediated pathway will be tested using the distribution of products test [63].

3.3. Aim 3—We will investigate whether baseline PTSD severity moderates the advantage of IPST over SC on abstinence by adding the interaction between baseline PTSD severity and treatment condition as an additional predictor in the GLMM in Aim 1. We expect that the improved abstinence in IPST over SC will be greater for those with higher levels of baseline PTSD severity.

3.4. Missing data—Following Hall et al. [33] and Enders ([22], p. 201), we will use pattern mixture modeling to assess the effect of missing data. We will rerun our analyses coding for various missing data patterns (no missing data, sporadic missing, dropouts, etc.) to determine both if missingness impacts our findings and how the differences between IPST and SC depend on the missing data pattern.

4. Discussion

Smokers presenting with PTSD are particularly vulnerable to smoking cessation failure yet little attention has been paid in the treatment literature to this at-risk group. Currently, no targeted smoking cessation treatments for smokers with PTSD exist despite this need for such an intervention. Thus, the goal of the present study is to evaluate the potential efficacy of an integrated approach to smoking maintenance, combining cognitive-behavioral therapy and NRT for smoking cessation with Prolonged Exposure therapy to target PTSD symptoms and interoceptive exposure to reduce anxiety sensitivity and distress intolerance.

The results of the proposed study will have implications for the utility of a personalized smoking cessation intervention for individuals with PTSD with regard to the reduction of PTSD symptoms and smoking behavior. In addition, the expected findings should 1) provide information regarding key mechanisms by which this integrated approach improves smoking cessation outcomes; and 2) provide effect size data, which will be used to estimate the

sample size to conduct a full-scale trial. The decision to pursue a full-scale trial will be informed based on the findings in Hypothesis 1A. More specifically, if the point prevalence abstinence (PPA) is significantly higher in the IPST condition than in the SC condition, we will initiate a full-scale trial.

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Session	Baseline	Treatment			Follow-ups			
			Quit Week		1st	2nd	3rd	4th
Weeks	0	1 to 5	6	7 to 12	14	16	22	30
Follow-up schedule from end of treatment					2wk	1m	2.5m	4.5m
Follow-up schedule from Quit Week					2m	2.5m	4m	6m

Fig. 1.
Treatment and Follow-up Schedule.

Fig. 2.
Mediation Model.

Table 1

Schedule of assessments.

Protocol weeks		>-3	-2	0	1 to 5	6	7 to 12	14,16,22,30
Measures		Pre-screen	Screening	Baseline	Treatment	Quit week	Treatment	Follow-ups
Screening								
Demographics		X	X					
General health history		X						
SCID			X					
C-SSRS			X					
Reasons for quitting smoking			X					
SHQ			X					
Consequence to smoking cessation			X					
BDI				X				
Motivation to quit smoking				X	X	X	X	X
Behavior rating scale				X	X	X	X	X
Smoking outcomes		X	X	X	X	X	X	X
Point-prevalence abstinence				X	X	X	X	X
Prolonged abstinence				X	X	X	X	X
Timeline follow-back				X	X	X	X	X
Carbon monoxide				X	X	X	X	X
Saliva cotinine				X	X	X	X	X
Nicotine dependence and withdrawal							X	X
SAEQ		X		X				
FTND		X		X				
QSU			X					
PTSD severity				X	X	X	X	X
PDS				X	X	X	X	
PTCI				X	X	X	X	X
PSSI				X	X	X	X	X
Anxiety sensitivity & distress intolerance				X				X
ASI-III		X	X	X	X	X	X	X

	Protocol weeks					
DTS	X			X	X	X
AIS				X	X	X
Treatment acceptance				X		
CEQ				X		

Table 2

Session-by-session outline of intervention procedures.

Week	SC	IPST
Baseline		<ul style="list-style-type: none"> Standardized trauma
1	<ul style="list-style-type: none"> Provide quit support and reinforcement Discuss past experiences Set quit date (first day of week 6) Initiate self-monitoring (tracking smoking and noting cues for smoking) 	<ul style="list-style-type: none"> Integrated treatment (IPST) rationale Education on PTSD-smoking link Interoceptive exposure practice
2	<ul style="list-style-type: none"> Cognitive restructuring Rationale for tapering 	<ul style="list-style-type: none"> Homework practice review Common reactions to trauma Interoceptive exposure practice
3	<ul style="list-style-type: none"> Help identify high-risk for relapse situations 	<ul style="list-style-type: none"> Homework practice review Interoceptive exposure practice Homework practice assigned
4	<ul style="list-style-type: none"> Develop alternative coping strategies Encourage enlisting social support Provide self-help materials 	<ul style="list-style-type: none"> Homework practice review Rationale for in-vivo exposure Construct in-vivo hierarchy Homework practice assigned Instruction to refrain from smoking 4 h prior to session
5	<ul style="list-style-type: none"> Discussion of upcoming quit day Discussion of environmental control Instruct on proper use of NRT 	<ul style="list-style-type: none"> Homework practice review Rationale for imaginal exposure Imaginal exposure to trauma memory Cognitive restructuring & processing Homework practice assigned
6 Quit day	<ul style="list-style-type: none"> Initiate NRT Discussion of quitting experiences Provide support Create Abstinence Plan Anticipate high-risk situations Discussion of abstinence violation effect 	<ul style="list-style-type: none"> Homework practice review Encourage self-awareness of the role of PTSD symptoms in smoking behavior and urge to smoke. Underscore importance of integrating exposure, non--catastrophic thinking, and education to maintain abstinence. Imaginal exposure to trauma memory Cognitive restructuring & processing Homework practice assigned
7	<ul style="list-style-type: none"> Continue NRT Provide support Anticipate high-risk situations Lifestyle changes (e.g. stress management, exercise, and increasing pleasant nonsmoking activities) 	<ul style="list-style-type: none"> Homework practice review Imaginal exposure to trauma memory Cognitive restructuring & processing Homework practice assigned

Week	SC	IPST
	<ul style="list-style-type: none">• Discussion of resumption thoughts	
8–12	<ul style="list-style-type: none">• Continue NRT• Provide support	<ul style="list-style-type: none">• Homework practice review• Imaginal exposure to trauma memory• Processing• Homework practice assigned

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